Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Please cancel claims 15, 19-20, 24, 26-29, 32-33 and 35 without prejudice. Please amend claims 13, 17, 21-22, 30-31, 34 and 36 as below:

Claim 1. (Withdrawn) A method for elevating the plasma level of high density lipoprotein (HDL) in a mammal, said method comprising administering to said mammal an HDL-elevating, therapeutically-effective amount of an LXRβ selective agonist.

Claim 2. (Withdrawn) The method of Claim 1 further comprising administering to said mammal an additional active agent selected from the group consisting of an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: a cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a *beta*-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; insulin; phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

Claim 3. (Withdrawn) A method for elevating the plasma level of high density lipoprotein (HDL) in a mammal, without elevating the plasma level of triglycerides, said method comprising administering to said mammal an HDL-elevating, therapeutically-effective amount of an LXRβ selective agonist.

Claim 4. (Withdrawn) A method of decreasing the absorption of dietary cholesterol in the intestine of a mammal, said method comprising administering to said mammal an absorption-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

Claim 5. (Withdrawn) A method of elevating HDL-associated gene expression in a cell, said method comprising administering an LXRβ selective agonist to said cell.

Claim 6. (Withdrawn) The method of Claim 5 wherein the gene is encoded by a protein or polypeptide selected from the group consisting of ABCA1, ABCG1, CYP7A, ApoE, lipoprotein lipase, and a proinflammatory gene.

Claim 7. (Withdrawn) A method of decreasing the plasma level of low density lipoprotein (LDL) in a mammal, said method comprising administering to said mammal an LDL-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

Claim 8. (Withdrawn) A method of decreasing the plasma level of low-density lipoprotein (LDL) in a mammal, without elevating the plasma level of triglycerides, said method comprising administering to said mammal an LDL-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

Claim 9. (Withdrawn) A method of lowering the plasma level of low-density lipoprotein (LDL) in a mammal by increasing the conversion of cholesterol to bile acids, said method comprising administering a cholesterol-converting, therapeutically-effective amount of an LXRβ selective agonist.

Claim 10. (Withdrawn) A method of identifying an LXRβ selective agonist comprising:

a) selecting a candidate compound;

b) testing the candidate compound in a cell-based or biochemical assay that measures the LXRα and LXRβ agonist activity of the compound; and

c) identifying those candidate compounds which are LXRβ selective agonists as those compounds whose potency is lower for LXRβ as compared to LXRα; and/or whose efficacy is higher for LXRβ as compared to LXRα.

Claim 11. (Withdrawn) A method of identifying an LXRβ selective agonist comprising:

a) selecting a candidate compound;

b) contacting the candidate compound with a cell expressing LXRβ only and a first reporter gene containing DNA sequences to which LXRβ binds; and also contacting the candidate compound with a cell expressing LXRα only and a second reporter gene containing DNA sequences to which LXRα binds;

c) determining if the candidate is an LXRβ agonist and/or an LXRα agonist by examining the ability of the compound to induce transcription of the reporter gene under control of LXRβ and LXRα; and

d) identifying those candidate compounds which are LXRβ selective agonists as those compounds whose potency is lower for LXRβ as compared to LXRα; and/or whose efficacy is higher for LXRβ as compared to LXRα.

Claim 12. (Withdrawn) The method of Claim 10 wherein the LXRβ selective agonist is also an LXRα antagonist.

Claim 13. (Currently Amended) A method for treating diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases hyperglycemia.

Claims 14-15. (Canceled)

Claim 16. (Original) The method of Claim 13 further comprising administering to said mammal an additional active agent selected from the group consisting of an antihyperlipidemic agent; a plasma HDL-raising agent; antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: a cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; insulin; phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

Claim 17. (Currently amended). A method of ~~preventing the onset of,~~ reducing the risk of developing, or the risk of recurrence of, diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases insulin resistance.

Claims 18-20. (Canceled)

Claim 21. (Currently Amended) A method for treating type II diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases hyperglycemia.

Claim 22. (Currently Amended) A method for treating type II diabetes in a mammal and reducing the cardiovascular complications of type II diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases insulin resistance.

Claim 23. (Original) The method of claim 22 further comprising administering an additional active agent selected from the group consisting of a sulfonylureas; a biguanides, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoids; a TNFa inhibitor; an a-glucosidase inhibitor; pramlintide; an insulin secretogogues; and insulin.

Claims 24-29. (Canceled)

Claim 30. (Currently Amended) ~~The method of claim 13~~ A method for treating diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases insulin resistance.

Claim 31. (Currently Amended) ~~The method of claim 17~~ A method of reducing the risk of developing, or the risk of recurrence of, diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said method decreases plasma glucose levels.

Claims 32-33. (Canceled)

Claim 34. (Currently Amended) ~~The method of claim 21~~ A method for treating type II diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases insulin resistance.

Claim 35. (Canceled)

Claim 36. (Currently Amended) ~~The method of claim 22~~ A method for treating type II diabetes in a mammal and reducing the cardiovascular complications of type II diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist, wherein said treatment decreases hyperglycemia.

REMARKS/ARGUMENTS

Claims 1-13, 15-17, 19-24 and 29 to 36 were pending before this communication. By this response, claims 15, 19, 20, 24, 26-29, 32, 33, and 35 have been cancelled without prejudice, claims 13, 17, 21, 22, 30, 31, 31, 34 and 36 have been amended, to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and original claims. Specifically claim amendments to claims 13, 17, 21, 30, 31, 34 and 36 are supported, for example, by original claim 20, as well as paragraph 18 on page 5 of the specification and claims 29 to 36.

Withdrawal of certain rejections

Applicants acknowledge that the previous rejection of claims 21 and 22 under 35 U.S.C. 102(a) as being anticipated by Shan et al. (WO 01/03705) has been withdrawn.

Applicants further acknowledge that the previous rejection of claims 21 to 23 under 35 U.S.C. 103(a) as being obvious over Shan et al. (WO 01/03705) taken in light of Piper (US 2002/0177602 A1) has been withdrawn.

Claim Objections

Claims 16 and 23 are currently objected to because the claim contains recitation of non-elected "additional active agents." The Examiner has stated that each active agent is considered patentably distinct because each agent is different structurally and has different function and utility.

Applicants point out that claims 16 and 23 are dependent claims that define a Markush class of additional active agents to be used in combination with the LXR agonist method of the invention. Therefore, the additional active agents are not the focus of the invention, but are secondary agents used with the claimed methods. For the most part, these agents are existing and known compounds or biologics for use in these types of therapies. As a result, Applicants assert that this Markush class does not present a search burden, and further under MPEP 803.02 the election of "thiazolidinedione" is a species election within a Markush group structure. Respectfully, Applicants request the withdrawal of the objection to claims 16 and 23.

Issues under 35 U.S.C. §112, first paragraph

Claims 13, 16-17, and 21-23 and 29-36 have been rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled for a method for treating or preventing diabetes or treating type II diabetes. Applicants respectfully traverse the rejection on the grounds that the currently pending claims are fully enabled by the present specification.

The Examiner contends that the specification does not enable the method of treating or preventing type II diabetes with the administration of an LXR agonist. The Examiner further contends that the specification only discloses "cursory conclusions (page 4) without data supporting the findings" that LXR agonists provide methods for treating or preventing diabetes.

Applicants respectfully disagree and point to the examples on pages 30-39 of the application and the drawings (Figures 1-15) which provide data supporting the findings that LXR may prevent, halt or slow the progression of type II diabetes, using an in vivo animal model.

Applicants identified paragraph [0121] and Figure 15, for disclosures enabling claims to methods of treating type II diabetes with an LXR agonist. In the disclosed experiment, the pan LXR agonist, Compound 1, was administered to a mouse model of type II diabetes, the (*db/db*) mouse, which displays diabetic symptoms such as obesity and severe hyperglycemia (elevated blood glucose). The data shows that administration of the pan LXR agonist to the diabetic mouse results in significant reduction in hyperglycemia (Figure 15), and Applicants have therefore shown that the LXR agonist is an effective therapy for the treatment of type II diabetes.

Second, in contrast to the Examiner's assertion to the contrary, numerous LXR agonists are known in the literature and available for use in the claimed methods without undue experimentation. For example, at least six publications or patents were available at the effective filing date of the current application that disclose a wide range of oxysterol derivatives and synthetic LXR agonists.

U.S. Patent No. 5,607,967 to Friedman et al., entitled "Treatment of Alzheimer's disease with 5-(Tetradeccyloxy)-2-furan carboxylic acid," which issued March 4, 1997, discloses the compound TOFA (5-(Tetradeccyloxy)-2-furan carboxylic acid) as a regulator of the steroid receptor NER (which is an alternative early literature name for LXR).

U.S. Patent No. 6,184,215 to Elias et al., entitled "Treatment of skin conditions with oxysterol activators of LXR alpha," which issued February 6, 2001, discloses a variety of oxysterol activators of LXR.

PCT publication WO 98/32444 to Elias et al., entitled "Use of FXR, PPARα and LXRα activators to restore barrier function, promote epidermal differentiation and inhibit proliferation", which published July 30, 1998, discloses numerous oxysterol activators of LXR and their therapeutic use in epidermal differentiation and proliferation.

PCT publication WO 00/54759 to Li et al., entitled "LXR Modulators", published 21 September 2000, discloses a large number of LXR modulators.

PCT publication WO 00/66611 to Liao et al., entitled "Steroid Derivatives", published November 9, 2000, discloses a large number of steroid derivatives that act as LXR agonists.

PCT publication WO 01/03705 to Shan et al entitled "Compositions and methods for raising HDL cholesterol levels" discloses numerous LXR agonists.

PCT publication WO 01/41704 to Sparrow et al., entitled "Method for the prevention and/ or treatment of atherosclerosis," published June 14, 2001, discloses steroid and non steroid LXR agonists.

Therefore, a variety of agonists were available at the effective filing date of this application, thus establishing enablement.

Applicants cite *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) for the proposition that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art (see also, MPEP 2164.03). Applicants respectfully assert that methods of administering drugs for the treatment or prevention of diabetes with an identified class of compounds and given the prevalence of diabetic therapies are within the purview of a clinician of ordinary skill in the art, and therefore need not be provided, although general dosage information may be found in paragraphs [0061]-[0075] of the specification (see also MPEP 2164.01(c)).

For the above reasons, Applicant respectfully traverse Examiner's rejection under 35 U.S.C. §112, first paragraph for lack of enablement.

Applicants also respectfully traverse the Examiner's contention that the specification allegedly necessitates undue experimentation. The Examiner presented an undue experimentation analysis based on the six factors presented in *In re Wands* (858 F.2d at 731,737, 8 USPQ2d at 1400, 1404 (Fed. Cir. 1988)).

Applicants therefore respectfully submit a rebuttal under each factor.

(1) The breadth of claims: The currently pending claims specifically define the particular metabolic disease (diabetes) and are directed to the use of LXR agonists. The claims in question are directed to methods of using LXR agonists which agonists were known and described at the time the current specification was filed.

(2) The absence or presence of working examples: Applicants respectfully direct the Examiner's attention again to the experiments described on pages 30-39 and the drawings (Figures 1-15), which serve to differentiate the physiological effects of LXR ligands on various mouse disease models. Therefore, the burden is now on the Examiner to show by preponderance of the evidence that the specification is non-enabling, as determined on the totality of the record.

(3) The state of the prior art and relative skill of those in the art: Numerous LXR agonists existed prior to the filing of the current specification and were available to a person of ordinary skill in the art without experimentation. See *In re Wright*, 27 USPQ 2d 1510 (Fed. Cir. 1993).

(4) The amount of direction or guidance presented and the quantity of experimentation necessary: In the experiments conducted on animal disease models (see Paragraphs [0105]-[0122] and Figures 1-15), Applicants have for the first time established a direct correlation between LXR agonist activity and the amelioration of the symptoms of type II diabetes and atherosclerosis, thereby providing guidance and new impetus for the development of additional LXR agonists methods. Applicants also point out that methods of administering drugs for the treatment or prevention of diseases are within the purview of a clinician of ordinary skill in the art, and therefore need not be provided, although general dosage information may be found in paragraphs [0061]-[0075] of the

specification. See MPEP 2164.02 as well as *In re Brana* 34 USPQ 2d 1436 (Fed. Cir. 1995) and *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985).

(5) Predictability or unpredictability of the art: The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (see MPEP§ 2164.03). In response to Examiner's contention that the invention is highly unpredictable regarding the outcome of the treatment, Applicants respectfully point to the experimental data showing the reduction of blood glucose in the diabetic mouse study, and the numerous LXR agonists that are known.

(6) Nature of the Invention: Applicants respectfully direct the Examiner to Applicants' arguments under sections (1), (2) and (3) to refute Examiner's claim that the specification does not show how diabetes is treated using an LXR selective agonist. Accordingly, it is Applicants position that based on the teachings of the specification, which the Examiner acknowledges enables practice of the claimed method with the disclosed species, the ordinary skilled artisan would be able to make and use the claimed methods without undue experimentation.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of pending claims 13, 16, 17, 21-23, 30-31, 34 and 36 under 35 U.S.C. §112, first paragraph, since the specification is enabling for the claimed methods.

Issues under 35 U.S.C. §112 second paragraph.

The Examiner has rejected claims 13, 16, 17, and 21-23, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection based on the grounds that the currently pending claims both particularly point out, and distinctly claim the subject matter that Applicants consider their invention.

However, in order to reduce issues and expedite prosecution, claims 13, 16, 17 and 21-23 have been amended to include the outcome of the method of treatment as recited in claims 29, 32, 33 and 35 and those corresponding claims have been canceled without prejudice.

In view of the foregoing amendments, Applicants respectfully requests reconsideration and withdrawal of this rejection of claims 13, 16, 17, and 21-23 under 35 U.S.C. §112, second paragraph.

Rejection of Claims Under 35 U.S.C. §102(b)

Claim 13 has been rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Shan *et al.*, (WO 01/3705, Jan. 2001). Applicants respectfully disagree.

Shan *et al.* does not teach a method of treating diabetes in a mammal by administering a therapeutically effective amount of an LXR agonist and accordingly cannot anticipate the claimed invention. The Examiner indicated in the Office Action that Applicants' prior arguments were partially persuasive and the rejection of claims 21 and 22 was withdrawn. It was implied that reciting the "outcome of treatment" in claim 13 would overcome this rejection.

Therefore, in order to reduce issues and expedite prosecution, claim 13 has been amended to clarify that the outcome of treatment, as recited in dependent claim 29, is to decrease hyperglycemia. Accordingly, Applicants thus respectfully request withdrawal of this rejection of claim 13.

Rejection of Claims Under 35 U.S.C. §103(a)

Claims 13 and 16 have been rejected under 35 U.S.C.§103(a) as allegedly being unpatentable over Shan *et al.* in light of Piper (US Application No. US2002/0177602 A1). Applicants respectfully traverse.

Claim 13 has been currently amended to clarify that the outcome of the claimed method is to decrease hyperglycemia. As discussed above, Shan *et al.* neither discloses, nor suggests the use of an LXR agonist for treating type II diabetes, or specifically a method for decreasing hyperglycemia. By contrast, Shan *et al.* teaches the use of LXR agonists to raise plasma HDL as a means of preventing or treating atherosclerosis and associated diseases.

Piper only teaches the use of thiazolidinedione as an antidiabetic agent.

Applicants accordingly request withdrawal of this rejection of claim 13 and dependent claim 16.

PREVIOUSLY SUBMITTED IDS

Applicants would appreciate receiving an acknowledgment of the Information Disclosure Statement, mailed June 11, 2003, in the next communication.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6108.

Respectfully submitted,

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